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Aminoalkoxybiphenylnitriles as Histamine-3 Receptor Ligands

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Abstract—Biaryl nitrile amines were prepared and found to have high affinity and selectivity for human and rat histamine H_3 receptors.

Histamine exerts a variety of physiological effects via four known distinct G-protein coupled receptors.[1] Histamine plays a major role in immediate hypersensitivity reactions following release from mast cells. The action of released histamine on airway and blood vessel smooth muscle accounts for the symptoms of the allergic response and is mediated by the H_1 receptor[2] and is blocked by classic antihistamines. Histamine is also an important regulator of gastric acid secretion through its action on parietal cells. These effects are mediated via the H_2 receptor[3] and these are blocked by H_2 receptor antagonists. The third histamine receptor[4] was first described as a presynaptic autoreceptor in the CNS controlling the synthesis and release of histamine. Recently, evidence suggesting the presence of H_3 receptors located presynaptically on hetero-receptors has emerged. The bulk of medicinal chemistry with respect to H_3 receptor ligands is related to their potential to treat CNS disorders. Some H_3 antagonists have been studied in models of learning, memory and schizophrenia.[5] Therefore a H_3 antagonist with high receptor selectivity and good BBB penetration may offer a new approach for the treatment of a wide range of CNS disorders. Recently we have described the SAR of a new series of non-imidazole containing H_3 blockers[6] (Fig. 1). In order to expand the SAR to provide a new isostere for the ketone moiety seen in Figure 1 and to optimize lipophilicity for CNS penetration, we prepared a series of biaryl piperazine amides.

We wish to report herein on the preparation and SAR of this series. Commercially available 4-bromophenol was treated with 1-bromo-3-chloropropane in the presence of K_2CO_3 in refluxing 2-butanone for 24 h (Scheme 1). The resulting *O*-propyl chloride (obtained in ~95% yield) was further treated, without purification, with piperazine-1-carboxylic acid ethyl ester to give the desired compounds (**1**) in 70–90% yield after silica gel chromatography. Treatment of **1** under Suzuki or Stille cross coupling reactions leads to the desired *N*-ethylcarbamate piperazine derivatives. These were assayed in a binding experiment using rat cortex in order to probe the SAR of the H_3 receptor.

Data from Table 1 indicate weak to moderate affinity for the rat H_3R, especially when compared with their alkylketone homologues.[6] However, based on favorable physicochemical properties and moderate potency, the biarylnitrile **4** was selected for further modification. The basic piperazine in **4** was replaced with a variety of amines (Scheme 2): morpholine, pyrrolidine, homopiperazine, 4-(*R*)-aminopyrrolidine, pyrrolidine[3,4-c]pyrrolidine,[9] etc., this time with significant improvement in affinity at the rat H_3R (e.g., compd **21** and **32** with pK_i of 8.01 and 8.19, Table 2) when compared to similar transformations in the alkylketone series.[6] Small alkyl-substituted pyrrolidines and piperidines provided for an enhanced affinity at the rat H_3R. From the data

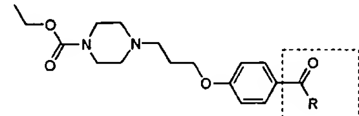

Figure 1.

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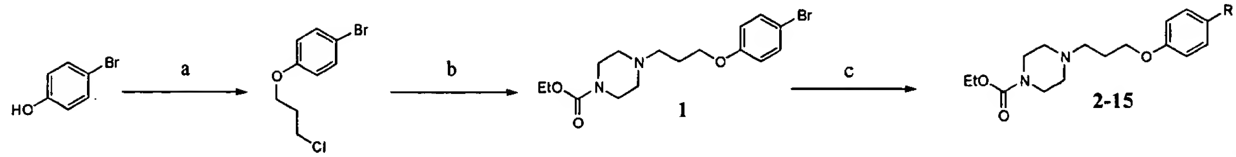
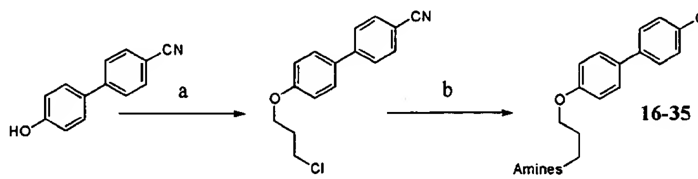


Scheme 1. (a) Cl–$(CH_2)_3$–Br, K_2CO_3, 2-butanone, reflux 24 h; (b): N–COOEt-piperazine, KI/K_2CO_3, 2-butanone, reflux 72 h; (c): Suzuki or Stille, $PdCl_2(Ph_3)_2$, DMF, 24 h, 40–75%.



Scheme 2. (a) Cl–$(CH_2)_3$–Br, K_2CO_3, 2-butanone, reflux 24 h, 98%; (b) amines, KI/K_2CO_3, 2-butanone, reflux 72 h, 60–90%.

Table 1. Binding affinities[a] (pK_i) at rat cortical H_3 and human H_1 and H_2 receptors[7,8]

Compd[b]:R	H_3	H_1	H_2	R	H_3	H_1	H_2
2: 4′-Br-Ph	6.95	6.74	5.78	**9**: 4-Pyridine-4	5.56	5.43	4.24
3: 4′-OMe-Ph	6.59	6.45	4.00	**10**: 4-Thiophen-2	6.64	6.35	4.48
4: 4′-CN-Ph	7.55	6.80	4.54	**11**: 4-Thiopen-3	6.68	6.12	4.01
5: 4′-Cl-Ph	6.72	6.45	5.25	**12**: 4′-OCF_3-Ph	6.62	6.36	5.44
6: 4′-NO_2-Ph	7.01	7.09	5.08	**13**: 4′-CN-2′-Me-Ph	6.99	7.56	5.40
7: 2′-NO_2-Ph	6.21	6.79	5.12	**14**: 4-Pyrrol	7.25	6.30	4.89
8: 3′-CN-Ph	5.95	6.42	4.62	**15**: 4-Imidazol	6.06	5.83	4.16

[a]Values were estimated from at least three separate competition experiments (SEM ≤ 0.2).
[b]Satisfactory ^{1}H NMR, MS spectra and elemental analyses were obtained for all new compounds.

in Table 2 the stereoselective nature of the H_3 receptor (e.g., compound **27** statistically significantly more potent than the *S*-enantiomer **28** at both rat ($P = 0.14$, unpaired *t*-test, RS/1) and human [$P = 0.04$, unpaired *t*-test, RS/1, see below] receptors) is noteworthy.

While this work was in progress Lovenberg and colleagues reported the cloning of the human H_3 receptor.[10] Subsequently, both the guinea pig and rat H_3 receptor orthologues have also been successfully cloned.[11] We assayed using human cloned H_3 receptors in binding experiments selected examples of the biarylnitrile series to explore their SAR at the human receptor (Table 3).

Some interesting observations can be made from these results: several *N*-ethylcarbamate piperazine compounds such as **4** and **14** were an order of magnitude less potent at the human recombinant receptor than at the native rat receptor (pK_i of 6.00 versus 7.55 or 6.00 versus 7.25 at human or rat H_3, respectively). The rat

Table 2. Binding affinities[a] (pK_i) at rat cortical H_3 and human H_1 and H_2 receptors

Amines	H_3	H_1	H_2	Amines	H_3	H_1	H_2
16: Piperazine	6.23	5.05	4.64	**26**: Pyrrolidine	7.38	5.30	4.17
17: Homopiperazine	7.87	5.41	5.11	**27**: 3-(*R*)-OH-Pyrrolidine	7.29	5.35	4.77
18: Morpholine	7.60	5.49	4.42	**28**: 3-(*S*)-OH-Pyrrolidine	6.90	5.25	4.72
19: 2-Me-Piperidine	7.64	5.46	4.73	**29**: 3-(*R*)-NH_2-Pyrrolidine	7.20	4.86	5.13
20: 3-Me-Piperidine	7.58	6.56	4.93	**30**: 3-(*R*)-NHMe-Pyrrolidine	7.53	5.43	5.00
21: 4-Me-Piperidine	8.01	6.37	5.04	**31**: 3-(*R*)-NMe_2-Pyrrolidine	7.87	5.72	5.00
22: 3-OH-Piperidine	7.09	5.11	4.89	**32**:2,5-(*R*,*R*)-di-Me-Pyrrolidine	8.19	6.25	5.04
23: 4-OH-Piperidine	7.50	6.24	5.00	**33**: 3-(*R*)-Me-Pyrrolidine-3-ol	7.81	5.41	4.82
24: 2,6-di-Me-Piperidine	7.79	5.40	4.62	**34**: Pyrrolidine[3,4-c]Pyrrolidine	7.18	5.54	4.91
25: 4-NH_2-Piperidine	6.89	5.45	4.47				

[a]See corresponding footnote in Table 1.

Table 3. Binding affinities[a] (pK_i) at human cloned H_3 receptors[10]

Compd	hH_3	Compd	hH_3	Compd	hH_3
4	6.00	**21**	7.86	**28**	7.71
14	6.00	**22**	7.52	**29**	8.21
16	6.93	**23**	6.91	**30**	8.07
17	8.08	**24**	8.67	**31**	8.56
18	7.44	**25**	6.70	**32**	9.17
19	8.15	**26**	8.14	**33**	8.39
20	8.77	**27**	8.08	**34**	7.82

[a]See corresponding footnote in Table 1.

H_3 receptor is highly homologous to the human receptor, although two amino acid residues differences located in the vicinity of the aspartate residue (Asp^{114}) in the TM3 helices important for the binding of positively charged biogenic amines could help explain these differences in binding between the two species. Ligneau and colleagues also observed these types of differences in binding with a number of H_3 antagonists.[12] In contrast, the biarylnitrile amines are displaying a reverse preference, that is, equipotent or an order of magnitude more potent at the human cloned receptor than at the rat receptor.

In summary we have discovered highly potent ligands for both human and rat H_3 receptors, with several exemplary compounds demonstrating an approximate 10-fold higher affinity for the human H_3 receptor. These results differ from a number of imidazole-based H_3 antagonists that show a weaker affinity for human, compared to rat H_3 receptors, such as thioperamide, ciproxifan or GT-2331.[13] The high affinity of some of these compounds (e.g., compd **31** or A-331440) for the human receptor, coupled with other favorable physiological and pharmacodynamic properties (to be described elsewhere),[14] suggest that such compounds may have therapeutic potential in various human diseases.

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